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COMPLETE SPECIFICATION

Vitamin-active powder and process for the manufacture thereof

We, ROCHE PRODUCTS LIMITED, a British Company, of Broadwater Road, Welwyn Garden City, Hertfordshire, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to dry, free-flowing powders containing a fat-soluble vitamin-active material, such powders being vitamin-active and useful for administration as such and also for the formulation of pharmaceutical dosage forms, e.g., tablets, capsules and powders, and for the preparation of animal feeds, and to a novel process for making such vitamin-active powders.

An important object of the invention is to provide a vitamin-active preparation in the form of a dry free-flowing powder characterised by high stability and high potency. A further object is to provide such a preparation which shall be suitable for incorporation in pharmaceutical formulations. A still further object is to provide such a preparation in which the proportion of non-active ingredients to vitamin-active material is as low as possible, having regard to the requirement for a dry, stable, highly potent powdered form.

It has been found, according to the process of the invention, that compositions of matter of the kind referred to hereinbefore can be made by introducing into a mass of starchy powder droplets of an emulsion in which the continuous phase is an aqueous solution containing a sugar or a sugar alcohol and gelatine or gum acacia and in which the disperse phase comprises the vitamin-active material, maintaining the vitamin-active particles formed in said powder separate from each other until their particulate form is established and separating said particles from said powder.

Briefly, the process comprises (1) forming an emulsion containing: (*a*) vitamin-active material, (*b*) water, (*c*) gelatin and/or gum acacia, and (*d*) a sugar and/or a sugar alcohol, (2) converting the emulsion to droplets, (3) collecting the individual droplets in a mass of starchy powder in such a manner that the vitamin-active particles formed from the droplets are kept separated from each other until their particulate form is permanently established and (4) separating the vitamin-active particles from the starchy collecting powder.

The starchy powder used to collect the droplets of emulsion can consist entirely of a starch and/or a starch chemically modified so as to impart to it in greater degree those characteristics found to be desirable in the collecting powder, as recited hereinbelow. The collecting powder may also contain, in addition to the starch and/or modified starch, minor amounts of lubricants and other modifiers, such as talc, silicic acid, flours, hydrogenated fats (e.g. "Sterotex", a hydrogenated vegetable oil product commercially distributed by Capital City Products, Columbus, Ohio, U.S.A.) and metal salts of higher fatty acids (e.g., calcium stearate). Whatever its composition, the collecting powder should possess the following characteristics: it should be substantially insoluble in cold water and, moreover, should be resistant to wetting by water; it should have an appreciable capacity to absorb and/or adsorb water; it should be free-flowing and it should have a low moisture content. The moisture content is particularly important and must be below about 8%, more desirably below about 6% and, in a preferred embodiment, below about 3%, e.g., in the range of about 1% and 3%. The desired moisture content can be easily attained by drying the commer-

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cially available starches or chemically modified starches.

In a preferred embodiment of the invention, the collecting powder consists substantially entirely of a starch modified to contain hydrophobic groups so as to possess the properties of free-flow and resistance to water-wetting to a higher degree than unmodified starch. Suitable modified starches may be prepared by reacting ungelatinised starch in an alkaline medium with a substituted succinic or glutaric acid anhydride, the substituent being an alkyl, alkenyl, aralkyl or aralkenyl radical (e.g. heptyl, nonenyl, octenyl, decenyl or octadecenyl), and reacting the starch acid-ester so formed with a compound containing a polyvalent metal ion (e.g. aluminium sulphate, ferrous sulphate, barium chloride, strontium nitrate, copper sulphate, ceric sulphate, chromic chloride or zinc chloride) in aqueous suspension and, finally, drying the product. A free-flowing starch ester, resistant to water-wetting, available commercially under the designation "Dry-Flo" and distributed by National Starch Products, Inc., New York, New York, U.S.A., has been found convenient to use as the specific starch ester for a preferred embodiment of the invention. As indicated, the "Dry-Flo" starch ester must be dried, to reduce its moisture content, before use.

Among the fat-soluble vitamin-active materials which can be used in practising this invention are vitamin-bearing oils, provitamins, pure or substantially pure vitamins (both natural and synthetic) or chemical derivatives thereof, crude products containing such substances and mixtures thereof.

The process of the invention is particularly applicable to the preparation of free-flowing powders containing vitamin A-active materials, more particularly vitamin A acetate or vitamin A palmitate, but it should be understood that the invention comprehends the preparation of powders containing any fat-soluble vitamin-active material, e.g., vitamins A, D, E or K and carotene or mixtures of such materials.

As stated hereinbefore, in practising the invention a first step comprises emulsifying the fat-soluble vitamin-active material with water, gelatin and/or gum acacia, and a sugar and/or a sugar alcohol. Among the sugars and sugar alcohols used in forming the emulsions employed herein are glucose, sucrose, partially inverted sucrose, sorbitol and mannitol. Antioxidants, such as tocopherols and butylated hydroxy-anisole; emulsifiers, such as lecithin; extenders and solubilisers, such as sesame oil and cottonseed oil; odour-imparting agents; colours; and other adjuvants conventionally used in pharmaceutical formulations, can also be incorporated in the emulsions.

The preparation of the vitamin-containing emulsion can be effected by methods which will be apparent to those skilled in the art. As an example of a method which has been found satisfactory, the following is mentioned: The gelatin and/or gum acacia are dissolved in water with the aid of moderate heating, and the vitamin-active substance is then dispersed or emulsified in the solution of the gelatin and/or gum acacia. The sugar and/or sugar alcohol, as well as any adjuvants, can be introduced into the mixture either before or after adding the vitamin-active material. The mixture is agitated until all dispersoids are uniformly distributed; if necessary, by passing the mixture through a homogeniser.

The introduction of droplets of the vitamin-containing emulsion into the collecting powder can likewise be effected by various methods which will suggest themselves to those skilled in the art. An important concept in the practice of this step of the invention is that of keeping the vitamin-active particles formed in the collecting powder by the emulsion droplets separated from each other for a long enough time so that they will "set up"; that is to say, the vitamin-active particles should be kept separated from each other until their particulate form is permanently established by loss of water, i.e., to such an extent that they will not agglomerate or coalesce during the most severe conditions of further processing, e.g., when the particles are spread out to dry on trays at about 45°C. The conversion of emulsion droplets to "set up" particles can be attained in various ways. For example, the emulsion droplets can be let fall by a moving nozzle upon a stationary layer of collecting powder at such a space interval that the droplets do not run together. Again the collecting powder can be presented as a moving layer (e.g., on a conveyor belt) below a fixed nozzle adjusted so as to allow the droplets to fall at a rate such that the droplets do not run together in the powder. Yet again, the emulsion droplets can be sprayed into an agitated mass of collecting powder (e.g., in a tumbler or in a vessel provided with a stirrer). The particular method employed is not of the essence of the invention. However, a preferred method comprises introducing a spray of emulsion droplets into an agitated cloud or suspension in air of the particles of collecting powder. A particular embodiment of this latter method which has been found useful in quantity production comprises forcing the emulsion through a revolving spray head having several rows of tiny orifices into an aerial suspension of the powdered starchy material contained in and agitated by a revolving cylindrical drum, the drum and the spray head rotating in opposite directions so that the cloud or suspension of the starchy powder in air is swirling

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in a sense of rotation opposite to the entering emulsion spray.

The separation of the vitamin-active particles from the collecting powder can be accomplished by operations which are conventional *per se*. It has been found convenient simply to feed the mixture of powder and vitamin-active particles to a shaking screen of a size selected to retain the vitamin-active particles while passing the collecting powder. It has been found advantageous to adjust the conditions under which the droplets of emulsion are formed (e.g., size of nozzle orifice, viscosity and percentage water content of emulsion) so that the final size of the vitamin-active particles is substantially entirely in the range which will pass through a 10-mesh screen and be retained upon a 150-mesh screen. A preferred size of vitamin-active particle for certain pharmaceutical compositions is in the range which will pass through a 40-mesh screen and be retained upon a 140-mesh screen. The starchy collecting powder is then selected to have a smaller particle size, i.e., the powder is substantially entirely in the range which will pass through a 150-mesh screen. It will be understood that for any desired size range of vitamin-active particle, the particles of collecting powder employed will be selected in a range of appreciably smaller size. A preferred size for the collecting powder is in the range which will pass substantially entirely through a 200-mesh screen.

The starchy collecting powder remaining after the screening step can be reused for further processing. After several " passes ", i.e., after the starchy powder has been used to collect several batches of emulsion droplets, the collecting powder will have picked up sufficient moisture to require a drying operation in order to reduce its moisture content to below about 8%.

The particles containing vitamin-active material formed in the collecting powder by the droplets of emulsion can be dried by various methods. The collecting powder itself effects a certain measure of drying in so far as it absorbs and/or adsorbs part of the water contained in the drops of emulsion, and this drying initiates the " setting up " phenomenon (i.e., the conversion of the droplet to a particle which will retain its particulate form even upon contact with other similar particles during further processing). The remaining water can be removed by various methods. For example, one can dry the entire mass (i.e., the collecting powder containing therein the vitamin-active particles), and then separate the collecting powder from the dried vitamin-active particles. It is preferred, however, to separate the vitamin-active particles shortly after they are formed in the powder, i.e., after their particulate form has been permanently established but before they are completely dry; and then to dry the vitamin-active particles substantially free of collecting powder; for example, by exposing them to air at *ca* 16°C. or by moderate heating in an oven, or by combinations of these and other suitable methods.

A typical powder produced by the process in question, when examined under a magnification of about 24 diameters, is seen to consist almost entirely of generally ovoid to spheroid-shaped particles of fairly uniform size. If a single particle is sectioned and stained with iodine and examined at a magnification of about 120 diameters it becomes apparent that the particle has a rather irregular surface, and that adhering to the surface of the particle are grains of the starchy collecting powder, stained dark by the iodine. Examination of various batches of vitamin-active powder produced according to the invention indicate that in no case does the proportion of the starchy collecting powder adhering to the vitamin-active particles, after separation of the same from the collecting powder and drying, exceed more than about 25-30% of the total weight of vitamin-active powder preparation, and that no fat-soluble vitamin is adsorbed on or absorbed in the starchy powder. Moreover, on continued screening of the vitamin-active powder, a portion of the adhering starchy powder can be shaken off, so that the final content of starchy powder can be reduced to not more than about 15% of the total weight of finished vitamin-active powder preparation. It is apparent, that the powders of the invention differ markedly from prior art " adsorbate " type vitamin powders, basically comprised of fat-soluble vitamins adsorbed on and absorbed in starch-containing granules. Presumably in consequence of their irregular surface and starchy powder coating, the dry vitamin-active powders produced by the processes of the invention have been found to possess advantages over prior art dry vitamin powders; e.g., ease and uniformity of mixing of the vitamin-active powder with other ingredients of pharmaceutical composition is facilitated; the " sticking " of such compositions containing the powder of the invention to tablet punches is obviated and the extrusion of the gelatin or gum acacia from tablets after compression is minimised.

The preferred form of the invention accordingly comprises introducing into a mass of starch powder droplets of an aqueous emulsion containing a fat-soluble vitamin-active material, maintaining the vitamin-active particles formed by said droplets in said powder separate from each other until their particulate form has been permanently established and separating from said powder the vitamin-active particles—said emulsion being one in which the continuous phase is an aqueous colloidal solu-

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tion containing as the principal solid constituents gelatin or gum acacia and sugars or sugar alcohols and in which the disperse phase comprises principally said fat-soluble vitamin-active material, said starch powder containing not more than about 8% moisture and predominantly composed of free-flowing starches or starch esters containing a hydrophobic group which are resistant to water wetting and have a particle size of substantially smaller dimensions than that of said vitamin-active particles. A preferred embodiment comprises introducing into an agitated cloud of starchy powder suspended in air droplets of an emulsion containing vitamin-A acetate, maintaining the particles formed by said droplets in said powder separate from each other until their particulate form has been permanently established and separating from said powder the vitamin-A-active particles—said emulsion being one in which the continuous phase is an aqueous colloidal solution containing as the principal solid constituents gelatine and sucrose and in which the disperse phase comprises principally vitamin-A acetate, said starch powder containing not more than about 3% moisture and being comprised predominantly of a free-flowing starch ester which contains a hydrophobic group and which is resistant to water wetting and which has a particle size substantially entirely finer than 200 mesh. The process of this embodiment should be so conducted as to allow the formation of vitamin-A-active particles which have a size substantially entirely within the range of from 140 mesh to 40 mesh.

It will ordinarily be desirable in practising the invention to use materials of at least pharmaceutical grade wherever possible.

The following examples are illustrative of the invention:

Example 1

100 g. of low bloom U.S.P. gelatin were dissolved in 100 g. of distilled water by heating to about 60°C. while stirring rapidly with a high speed stirrer under an atmosphere of nitrogen. 17.85 g. of crystalline vitamin-A acetate, assayed at 2.9 million I.U./g. vitamin-A activity, and previously melted at a temperature of about 65°C. under an atmosphere of nitrogen, were introduced into the solution. The mixture was stirred until the vitamin-A acetate was well dispersed. A solution of 20 g. of sucrose in 20 g. of distilled water, previously heated to 50°C. was then added while stirring. An additional 33 g. of distilled water previously heated to about 50°C. was added while stirring. The emulsion thus obtained was loaded into an apparatus provided with a revolving spray head and a counter-rotating drum, as above described. The drum was loaded with 2 kg. of "Dry-Flo", previously dried to a moisture content of about 3%. After all the emulsion had been collected in the "Dry-Flo", the mixture of starch and vitamin-active particles was allowed to stand for about an hour and was then screened through a 150 mesh screen. The vitamin-active particles retained upon the screen were collected, spread out on drying trays and then dried in an oven at 45°C. for 24 hours.

The dry, free-flowing powder containing vitamin-A acetate, thus obtained, had a particle size in the range of finer than 40 mesh and coarser than 150 mesh and assayed 250,000 I.U./g. of vitamin-A activity. Its "Dry-Flo" content was approximately 25% by weight. Upon continued screening of the vitamin-active powder on 150 mesh screens, the "Dry-Flo" content was reduced to about 16%, and the activity assay rose to about 273,000 I.U./g.

Example 2

100 g. of high bloom U.S.P. gelatin were dissolved in 150 g. of distilled water by heating to about 60°C. While stirring rapidly with a high speed stirrer under an atmosphere of nitrogen, 40 g. of crystalline vitamin-A acetate, assayed at 2.9 million I.U./g., and previously melted at a temperature of about 65°C. under a atmosphere of nitrogen, were introduced into the solution. The mixture was stirred until the vitamin-A acetate was well dispersed. A solution of 20 g. of sucrose in 20 g. of distilled water, previously heated to 50°C. was then added while stirring. An additional 90 g. of distilled water previously heated to about 50°C. was added while stirring. The emulsion thus obtained was loaded into an apparatus provided with a revolving spray head and a counter-rotating drum, as above described. The drum was loaded with 2 kg. of "Dry-Flo", previously dried to a moisture content of about 3%. After all the emulsion had been collected in the "Dry-Flo", the mixture of starch and vitamin-active particles was allowed to stand for about an hour and was then screened through a 150 mesh screen. The vitamin-A-containing particles retained upon the screen were collected, spread out on drying trays and then dried in an oven at 45°C. for 24 hours.

The dry, free-flowing powder containing vitamin-A acetate, thus obtained, had a particle size in the range of finer than 40. mesh and coarser than 150 mesh and assayed 500,000 I.U./g. Its "Dry-Flo" content was approximately 25% by weight.

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Example 3

133 g. of *d*-sorbitol and 25 g. of a low bloom U.S.P. gelatin were dissolved in 90 g. of distilled water by heating to about 90°C. The solution was cooled to 50°C. and, while stirring rapidly with a high speed mixer under an atmosphere of nitrogen, 25 g. of crystalline vitamin-A acetate, 2.9 million I.U./g., previously melted at a temperature of about 65°C. under atmospheric nitrogen, were introduced into the solution. The mixture was stirred until the vitamin-A acetate was well dispersed and was then passed through a homogeniser to obtain a uniform emulsion. The emulsion thus obtained was loaded into an apparatus provided with a revolving spray head and a counter-rotating drum, as above described. The drum was loaded with 1,500 g. of food grade corn starch, previously dried to a moisture content of about 3%. After all the emulsion had been collected in the starch, the mixture of starch and vitamin-bearing particles was allowed to stand for about 10 minutes and was then screened through an 80-mesh screen. The particles containing vitamin-A acetate retained upon the screen were collected, spread out on drying trays and exposed to air at room temperature for about 24 hours and then dried in an oven at 37°C. for an additional 24 hours.

The dry, free-flowing powder containing vitamin-A acetate thus obtained had an average size substantially entirely in the range of from about 30 mesh to about 40 mesh.

Example 4

In the manner described in the preceding example, an emulsion was formed containing 133 g. of *d*-sorbitol, 25 g. of vitamin-A palmitate (potency 1.8 million I.U./g.) and 30 g. of low bloom U.S.P. gelatin in 90 g. of distilled water. Before adding the vitamin-A palmitate, 0.52 g. of an antioxidant ("Tenox II", distributed by the Tennessee Eastman Co., Kingsport, Tennessee, U.S.A., containing butylated hydroxy anisole, propyl gallate, citric acid and propylene glycol) was also added to the mixture.

The emulsion thus obtained was formed into particles (average size: 30 mesh to 40 mesh) by means of the same apparatus and in the same manner as described in the preceding example.

Example 5

In a manner similar to that described in Example 3, an emulsion was prepared from the following ingredients: 266 g. *d*-sorbitol, 50 g. gelatin (low bloom, U.S.P.), 77 g. crystalline vitamin-A acetate (2.9 million I.U./g,) and 220 g. distilled water. Approximately 50 g. of the emulsion thus obtained was loaded into a hypodermic syringe having a 27 gauge needle and forced through the needle into 1,500 g. of "Dry-Flo" contained in an open vessel, while stirring the "Dry-Flo". After all the emulsion had been collected in the "Dry-Flo", the entire mixture was spread out in shallow drying trays and dried first in air at room temperature for 24 hours and then in an oven at 37°C. for 24 hours. The dried mixture was then screened through an 80-mesh screen and the vitamin-containing particles retained on the screen were collected.

Example 6

In a manner similar to that described in Example 3, a vitamin-A-active powder was prepared from the following ingredients: 108 g. *d*-sorbitol, 50 g. gelatin (low bloom, U.S.P.), 35 g. vitamin-A palmitate (potency 1.3 million I.U./g.), 2 g. mixed tocopherols (34% w/w), 6 g. of the alkyl aryl polyoxyethylene glycol which is marketed under the registered trade mark "Antarox 404" and distributed by Antara Products Division, General Dyestuff Corp., New York, New York, U.S.A., and 100 g. distilled water.

Example 7

In a manner similar to that described in Example 3, an emulsion was prepared from the following ingredients: 266 g. *d*-sorbitol, 50 g. gelatin (high bloom U.S.P.), 60 g. vitamin-A acetate (potency 2.3 million I.U./g.) and 135 g. distilled water. The emulsion thus prepared was formed into vitamin-A-active particles by a procedure similar to that described in Example 3, except that the collecting powder consisted of: 1,300 g. corn starch (food grade), 100 g. silicic acid and 100 g. calcium stearate (pharmaceutical grade).

Example 8

510 g. of low bloom U.S.P. gelatin were dissolved in 510 g. of distilled water by heating to about 60°C. The solution was cooled to 50°C.; and while stirring rapidly with a high-speed mixed under an atmosphere of nitrogen, 12.5 g. of calciferol (40 million I.U./g. vitamin-D activity), previously dissolved in 80 g. of U.S.P. sesame oil at 65°C. under atmosphere of nitrogen, were introduced into the solution. The mixture was stirred until the vitamin-D_2 sesame oil solution was well dispersed. A solution of 100 g. of sucrose in 100 g. of distilled water, previously heated to about 50°C., was then added while stirring. An additional 400 g. of distilled water, previously heated to about 50°C. was added while stirring. The emulsion thus obtained was loaded into an apparatus provided with a revolving spray head and a counter-rotating drum, as above described. The drum was loaded with 10 kg. of "Dry-Flo", previously dried to a moisture

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content of about 3%. After all the emulsion had been collected in the "Dry-Flo", the mixture of starch and vitamin-bearing particles was allowed to stand for about an hour and was then screened through a 120 mesh screen. The particles containing vitamin-D_2 retained upon the screen were collected, spread out on drying trays and then dried in an oven at 45°C. for 24 hours.

The dry, free-flowing powder containing vitamin D_2 thus obtained, had a particle size in the range of finer than 30 mesh and coarser than 120 mesh and contained 500,000 I.U./g. of vitamin D activity. Its "Dry-Flo" content was approximately 25%.

Example 9

50 g. of low bloom U.S.P. gelatin were dissolved in 50 g. of distilled water by heating to about 60°C. The solution was cooled to 50°C. and while stirring rapidly with a high-speed stirrer under an atmosphere of nitrogen, 10 g. of carotene (90% beta, 10% alpha; 1,670,000 I.U./g. vitamin-A activity) were introduced into the solution. The mixture was stirred until the carotene was well dispersed. A solution of 10 g. of sucrose in 10 g. of distilled water, previously heated to about 50°C., was added while stirring. An additional 95 g. of distilled water, previously heated to about 50°C. was added while stirring. The emulsion thus obtained was loaded into an apparatus provided with a revolving spray head and a counter-rotating drum, as above described. The drum was loaded with 1 kg. of "Dry-Flo", previously dried to a moisture content of about 3%. After all the emulsion had been collected in the "Dry-Flo", the mixture of starch and vitamin-bearing particles was allowed to stand for about an hour and was then screened through a 120 mesh screen. The carotene-containing particles retained on the screen were collected, spread out on drying trays and then dried in an oven at 45°C. for 24 hours.

The dry, free-flowing powder containing carotene, thus obtained, had a particle size in the range of finer than 30 mesh and coarser than 120 mesh and assayed 167,000 I.U./g. of vitamin-A activity. Its "Dry-Flo" content was approximately 25%.

What we claim is:—

(1) A process for the manufacture of free-flowing vitamin-active powders, which comprises introducing into a mass of free-flowing starchy powder having a moisture content of below about 8% droplets of an emulsion in which the continuous phase is an aqueous solution containing a sugar or a sugar alcohol and gelatine or gum acacia and in which the disperse phase comprises a fat-soluble vitamin-active material, maintaining the vitamin-active particles formed in said powder separate from each other until their particulate form is established and separating said particles from said powder.

(2) A process for the manufacture of free-flowing vitamin-active powders, which comprises introducing into a mass of starchy powder droplets of an emulsion in which the continuous phase is an aqueous colloidal solution containing as the principal solid constituents gelatin and/or gum acacia and a sugar and/or sugar alcohol and in which the disperse phase comprises principally a fat-soluble vitamin-active material, maintaining the vitamin-active particles formed by said droplets in said powder separate from each other until their particulate form is established, and separating from said powder the said vitamin-active particles—said starchy powder containing not more than *ca* 8% moisture and being predominantly composed of free-flowing starches or starch esters containing a hydrophobic group and resistant to water wetting and having a particle size of substantially smaller smaller dimensions than that of said vitamin-active particles.

(3) A process in accordance with Claim 1 or Claim 2, wherein the droplets of said emulsion are introduced into an agitated cloud of said starchy powder.

(4) A process in accordance with any one of the preceding claims, wherein the said starchy powder contains less than 6% of moisture.

(5) A process in accordance with any one of the preceding claims, wherein the fat-soluble vitamin-active material used is a vitamin-A-active or a vitamin-D-active material.

(6) A process in accordance with Claim 5, wherein the said vitamin-A-active material is a vitamin-A ester.

(7) A process in accordance with Claim 6, wherein the vitamin-A ester is vitamin-A acetate.

(8) A process in accordance with Claim 7, wherein the starchy material used contains less than 3% moisture.

(9) A process in accordance with any one of Claims 6 to 8 inclusive, wherein the emulsion used contains in its continuous phase gelatine and sucrose.

(10) A process in accordance with Claim 6, wherein the starchy powder used is a starch ester having a particle size substantially finer than 150 mesh—the process being conducted so as to allow of the formation of vitamin-A-active particles of a size substantially coarser than 150 mesh but finer than 10 mesh.

(11) A process in accordance with Claim 9, wherein the starchy powder used is a

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starch ester having a particle size substantially finer than 200 mesh—the process being conducted so as to allow of the formation of vitamin-A-active particles of a size substantially coarser than 140 mesh but finer than 40 mesh.

(12) A process for the manufacture of free-flowing vitamin-active powders, substantially as described with reference to the examples herein.

(13) Free-flowing vitamin-active powders when produced by the process claimed in any one of the preceding claims.

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